PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
13453-12PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/000493	02.04.2004	03.04.2003
International Patent Classification (IPC) or national classification and IPC		
A61K38/48, A61K38/36		
Applicant		
CANADIAN BLOOD SERVICES et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.02.2005	18.07.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000493

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-12	as originally filed
Claims, Numbers	
1-23	received on 03.02.2005 with letter of 03.02.2005
Drawings, Sheets	
1/3-3/3	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/CA2004/000493

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18,19

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 18,19

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000493

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17,20-23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17,20-23
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Concerning Section V:

The following prior art is cited from the International Search Report:

D1: EP-A-0 761 686
D2: EP-A-0 680 764
D3: EP-A-0 651 054
D4: WO 92/04378
D5: WO 91/02532
D6: GRUNDY J E, LAVIGNE N, HIRAMA T, MACKENZIE R, PRYZDIAL E L G: "Binding of Plasminogen and Tissue Plasminogen Activator to Plasmin-Modulated Factors X and Xa" BIOCHEMISTRY, vol. 40, no. 21, 29 May 2001, pages 6293-6302
D7: PRYZDIAL E L G, KESSLER G E: "Kinetics of Blood Coagulation Factor Xa alpha Autoproteolytic Conversion to Factor Xa beta" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 28, 12 July 1996, pages 16621-16626
D8: PRYZDIAL E L G, KESSLER G E: "Autoproteolysis or Plasmin-mediated Cleavage of Factor Xa alpha Exposes a Plasminogen Binding Site and Inhibits Coagulation" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 28, 12 July 1996, pages 16614-16620
D9: PRYZDIAL E L G, LAVIGNE N, DUPUIS N, KESSLER G E: "Plasmin converts factor X from coagulation zymogen to fibrinolysis cofactor" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 13, 26 March 1999, pages 8500-8505
D10: PRYZDIAL E L G; BAJZAR L; NESHEIM M E: "Prothrombinase Components Can Accelerate Tissue Plasminogen Activator-catalyzed Plasminogen Activation" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 30, 1995, pages 17871-17877

D1 describes anticoagulant factor Va derivatives. **D2**, page 3 lines 41-45 and claims 8 and 9 and **D3**, Examples disclose pharmaceutical preparations comprising Factor X, in particular Factor Xa, preferably Xa beta. **D4** describes analogues of Factor Xa which are useful in the treatment of thrombotic diseases. **D5** describes the endogenous stimulation of fibrinolysis by administering to a patient a mixture of Factor Xa and phospholipid vesicles. **D6**, **D7** and **D8** report Factor Xa gamma and Factor Xa beta, respectively, to be

fibrinolysis accelerators. **D6** also stresses that C-terminal lysine residues are well-known essential characteristics of plasminogen receptors. **D9** and **D10** report that plasmin converts procoagulant phospholipid-bound Faxtor Xa and Factor Va into fibrinolysis cofactors of t-PA.

The compositions known from D1-D5 are considered to anticipate the compositions claimed in present claims 20-23 since the intended use is not considered to be a feature capable of delimiting the claimed compositions from those known from the prior art. The ability of Factors Xa (alpha, beta and gamma) and Va to act as fibrinolysis accelerators is known from D1 and D4-D10. Furthermore, the expression "for accelerating blood clot dissolution" is not capable of delimiting the methods claimed from those of the prior art, since e.g. D1 which concerns the treatment of a hypercoagulant condition, thrombosis or thromboembolic disease states in column 7, linees 41-45 that "treating" refers to ".. curing, reversing, attenuating, alleviating ..". Therefore, novelty (Article 33 (2) PCT) cannot be acknowledged for the present claimed subject-matter.

If novelty can be established, then an inventive step (Article 33 (3) PCT) cannot be acknowledged since the principle of using coagulation proteins having a C-terminal lysine group in fibrinolysis is known from the prior art.

The expression "coagulation protein comprising a basic C-terminal amino acid" fails to define the substance envisaged according to the application and is also considered to lack support in description, since it is clear from the description that Factor Xa alpha, beta and gamma and Factor Va are envisaged. Therefore, the said expression is inadmissible under Article 6 PCT.

Methods of treating the human or animal body by therapy might be considered inadmissible.

I/WE CLAIM:

1. A method for accelerating blood clot dissolution in a subject in need thereof, the method comprising:

   a) administering to said subject at least one coagulation protein comprising a basic C-terminal amino acid in an amount effective to dissolve said blood clot.

2. The method as claimed in claim 1 wherein said protein is an anionic phospholipid-binding protein.

3. The method as claimed in claim 1 or 2 wherein said subject has a condition selected from: thrombosis, platelet hyperactivity, cardiac ischemia, wound, cardiovascular disease, atherosclerosis, myocardial infarction or a combination thereof.

4. The method as claimed in claim 3 wherein said subject is susceptible to said condition and said administering is prophylactic.

5. The method as claimed in claim 1 or 2 wherein said at least one coagulation protein is a derivative of Factor X.

6. The method as claimed in claim 5 wherein said derivative is selected from Factor Xaα, Xaβ, Xaγ, or a combination thereof.

7. The method as claimed in claim 1 or 2 wherein said at least one coagulation protein is a derivative of Factor V.

8. The method as claimed in claim 7 wherein said derivative is Factor Va.

9. The method as claimed in claim 1 or 2 wherein said at least one coagulation protein comprises a derivative of Factor X and a derivative of factor V.

10. The method as claimed in claim 5 wherein administering comprises administering to the subject a pharmaceutical composition comprising said derivative of Factor X and an acceptable carrier.

11. The method according to claim 10 wherein said derivative of Factor X is selected from Xaα, Xaβ and Xaγ or a combination thereof.

12. The method as claimed in claim 7 wherein administering comprises administering to the subject a pharmaceutical composition comprising said derivative of Factor V and an acceptable carrier.

13. The method according to claim 12 wherein said derivative of Factor V is selected from Va.

14. The method as claimed in any one of claim 10-13 wherein said pharmaceutical composition further comprises a fibrinolytic agent selected from tissue plasminogen activator, urokinase, streptokinase or a combination thereof.

15. The method as claimed in any one of claim 10-14 wherein said pharmaceutical composition further comprises an inhibitor of thrombin.

16. The method as claimed in claim 15 wherein said inhibitor of thrombin is selected from hirudin, bivalirudin, lepirudin and heparin or a combination thereof.

17. The method as claimed in claim 14 or 15 wherein said pharmaceutical composition is administered intravenously, intramuscularly, subcutaneously, intraperitoneously or intraarterially or a combination thereof.

18. A method for detecting a fibrinolytic potential in a subject the method comprising:

a) obtaining a blood sample from said subject; and

b) measuring a relative concentration of a coagulation protein selected from a coagulation protein comprising a basic C-terminal amino acid, a derivative of a coagulation protein comprising a basic C-terminal amino acid or a combination thereof.

19. The method as claimed in claim 18 wherein said coagulation protein is selected from a derivative of Factor X or Factor V.

20. A pharmaceutical composition comprising a coagulation protein for ~~the treatment or prophylaxis of blood clotting~~ accelerating blood clot dissolution wherein said coagulation protein comprises a basic C-terminal amino acid.

21. A pharmaceutical composition according to claim 20, wherein said coagulation protein is a derivative of Factor X or Factor V or a combination thereof.

22. A pharmaceutical composition according to claim 21, wherein said Factor X is selected from Xaα, Xaβ and Xaγ or a combination thereof, and Factor V is selected from Va.

23. A pharmaceutical composition according to any one of claims 20 to 22, and a pharmaceutically acceptable carrier, and/or one or more fibrinolytic agents, and/or one or more inhibitors of the coagulation pathway.